REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Pursuant to 37 CFR § 1.21, attached as an Appendix is a Version With Markings to Show Changes Made to the amended claims.

The rejection of claims 1-7, 10, and 41 under 35 U.S.C. § 112 (first paragraph) as lacking adequate written descriptive support for the term "target molecule" is respectfully traversed in view of the above amendments.

The rejection of claims 1-7, 10, and 41 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 4,980,473 to Barton et al. ("Barton") in view of U.S. Patent No. 5,958,703 to Benner et al. ("Benner") is rendered moot with respect to claim 41 and respectfully traversed with respect to claims 1-7 and 10.

Barton discloses the preparation of coordination complexes having the formula $(R)_3$--M, where M is a transition metal (e.g., Ru or Co), R is a 1,10-phenanthroline or substituted derivative thereof, and R is bonded to M by a coordinate bond.

Benner discloses a combinatorial library which contains two components (Ax and yB), each including a functional group which allows the two components to react directly together when presented with a ligand (see column 5, lines 26-61). In Example 5, however, Benner discloses the introduction of a borate ion into a solution which includes a beta lactamase and 1,2 diols, where the 1,2 diols react with the borate ion to form a combinatorial library of borate esters or orthoborate esters. However, this aspect of Benner does not involve a metal atom or metal ion and the diols do not form a labile coordinate bond with a metal atom or metal ion.

The U.S. Patent and Trademark Office ("PTO") has taken the position at page 5 of the outstanding office action that the coordination complexes of Barton could be prepared as a library and the resulting library screened since Benner "discloses the advantages of utilizing soluble 'combinatorial library' techniques for generat[ing] diverse structures which could then be advantageously screened e.g. using a 'receptor-assisted combinatorial chemistry'." Applicants respectfully disagree.

Applicants submit that Barton does not suggest the preparation of a library of coordination complexes. Specifically, Barton recites that R can be "1,10-phenanthroline or a

substituted derivatives thereof" (col. 7, lines 10-12), but not both; Barton recites that the substituted derivatives can be one of a laundry list of exemplary phenanthroline derivatives (col. 7, lines 12-27), but not combinations thereof; and although a racemic mixture of enantiomers is contemplated (col. 7, lines 27-29), Barton makes clear that the enantiomers are stereospecific enantiomers because of the asymmetric center of the cation used to form the coordination complex (col. 9, lines 25-55). Thus, Barton only suggests to one of ordinary skill in the art the formation of individual coordination complexes where each R group of the coordination complex is the same. For this reason, one of ordinary skill in the art would not have attempted to utilize the coordination complexes of Barton to form a combinatorial library in solution.

Even assuming *arguendo* that Barton does suggest the preparation of a library of coordination complexes *per se*, which applicants do not admit, the resulting library would not be the type of library recited in claim 1. Claim 1 recites, in pertinent part, that the library includes complexes where "each ... [is] formed of a metal atom or metal ion and at least two non-biopolymer ligands" with "each of the at least two non-biopolymer ligands [being] reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond" (emphasis added). In sharp contrast to the presently claimed invention, the complexes taught by Barton are not characterized by the presence of labile bonds. In fact, Barton teaches away from the formation of coordination complexes which include even a somewhat labile bond. Specifically, Barton, in specifying why the ruthenium(II) complexes have been found useful, states that "in contrast to $(phen)_3Zn^{2+}$, which is somewhat labile, the ruthenium(II) complexes are essentially inert to racemization" (col. 9, line 67 to col. 10, line 2). Thus, even if one of ordinary skill in the art were to form a combinatorial library of coordination complexes of the type taught by Barton, one of ordinary skill in the art would have been directed away from the use of metal atoms or metal ions which favor formation of labile coordinate bonds.

Benner fails to overcome these deficiencies of Barton. While Benner generally teaches the formation of combinatorial libraries which can be screened, Benner certainly does not suggest, either alone or in combination with Barton, the formation of a combinatorial library using a metal atom or metal ion and at least two non-biopolymer ligands each including at least one functional group, where the non-biopolymer ligands are reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond.

Nowhere does Benner or Barton provide any suggestion or other motivation for forming a combinatorial library with the use of a metal atom or metal ion which is capable of forming a labile coordinate bond with non-biopolymer ligands, and the PTO has failed to cite any other motivation in the prior art which would have suggested to one of ordinary skill in the art that it was desirable to do so. Because Barton and Benner, either individually or in combination, fail to teach or suggest each and every element of the presently claimed invention, Barton and Benner cannot have rendered obvious claims 1-7 and 10. Therefore, the rejection of these claims is improper and should be withdrawn.

The rejection of claims 1-7 and 41 under 35 U.S.C. § 102(b) as anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over Blackborow et al., "Redistribution Reactions of Some Transition-metal Chelate Complexes. Part III. Exchange in the Zinc Salicylaldimine Series," J. Chem. Res. (S) 119 (1978) ("Blackborow"), is rendered moot with respect to claim 41 and respectfully traversed with respect to claims 1-7.

Blackborow generally discloses the ability of salicylaldimines to form monomeric and polymeric complexes with zinc ions (i.e., "salicylaldiminatozinc derivatives" as used by Blackborow). However, the salicylaldiminatozinc derivatives are formed in a non-aqueous environment, specifically deuterated chloroform ($CDCl_3$) (see Blackborow, Table 2, note a).

In contrast to Blackborow, the combinatorial library of the present invention "exists at equilibrium in an aqueous solution or suspension including one or more metal atoms or metal ions and a group of three or more non-biopolymer ligands" and includes "a plurality of at least six different complexes in the aqueous solution or suspension, each of the plurality of at least six different complexes being formed of a metal atom or metal ion and at least two non-biopolymer ligands" (emphasis added). Nowhere does Blackborow teach the use of an aqueous solution or suspension for purposes of preparing or using the disclosed salicylaldiminatozinc derivatives. Because Blackborow fails to teach each and every limitation of claim 1, as well as claims 2-7 dependent thereon, Blackborow cannot anticipate the presently claimed invention.

Moreover, Blackborow fails to provide any motivation for making the disclosed salicylaldiminatozinc derivatives in an aqueous solution or suspension, let alone using the combinatorial library (for any purpose) in an aqueous solution or suspension. In particular, as noted in the previous response, Blackborow failed to recognize that any resulting salicylaldiminatozinc derivatives possessed activity in binding to a biological

receptor; thus, Blackborow provides no motivation for preparing the same in an aqueous solution. Blackborow also fails to provide one of ordinary skill with any expectation of success that such salicylaldiminatozinc derivatives would also form in an aqueous solution or suspension. Therefore, Blackborow would not have rendered the presently claimed invention obvious at the time the invention was made.

In view of all of the above, the rejection of claims 1-7 over Blackborow is improper and should be withdrawn.

The rejection of claims 1-7 and 10 under 35 U.S.C. § 102(a) as anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over WO 98/12156 to Jacobsen et al. ("Jacobsen") is respectfully traversed.

Jacobsen teaches a combinatorial library which includes a turn element and a plurality of metal-binding groups, whereby the resulting complex is capable of binding a metal ion. Jacobsen refers to these library members as "potential binding moieties" or PBM's (Jacobsen, page 2, line 1). After forming the library of PBM's, Jacobsen teaches exposing the library to metal atoms (Jacobsen, page 2, lines 1-2). Apparently, the PTO has taken the position that the library of PBM's, following exposure to metal atoms or ions, either anticipates or would have rendered obvious the presently claimed invention. Applicants respectfully disagree.

There are several key distinctions between the library of Jacobsen and the present invention.

Firstly, Jacobsen fails to teach a library as recited where each of the complexes of the library is "formed of a metal atom or metal ion and at least two non-biopolymer ligands" as recited, with "each of the at least two non-biopolymer ligands [being] reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond." Because the complexes of the presently claimed combinatorial library are formed by a labile bond, the complexes "exist[] at equilibrium in an aqueous solution or suspension including one or more metal atoms or metal ions and a group of three or more non-biopolymer ligands each of which comprises (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a biological receptor". This deficiency of Jacobsen is evident, because Jacobsen suggests utilizing assays for detection of PBM metal binding activity which would be unreliable, at best, if metal binding was labile (as in the present invention). At page 33, line 31 to page 34, line 26, Jacobsen suggests using either (i) colorimetric or fluorometric

detection schemes to identify substrate bound (i.e., immobilized) PBM's which have metal binding activity; (ii) detection of particular activities, such as catalyst activity, of the PBM's which are complexed with metals; or (iii) association of PBM's complexed to metal ions with labels that can be detected. These detection schemes all contemplate a non-labile relationship between the PBM's of the library and metal ions.

As further evidence that the PBM's complexed with metal ions are not intended to exist under equilibrating conditions with the components thereof, Figure 1 illustrates the preparation of the PBM library in a first step where combinatorial synthesis occurs and then, in a second distinct step, introduction of a metal source to the PBM library alone, as opposed to a mixture of the PBM library and the library of modular components.

Secondly, combinatorial synthesis of the PBM library in Jacobsen cannot occur in aqueous solution or suspension as recited in the presently claimed invention. The section of Jacobsen entitled "VI. Reaction Conditions" is not instructive, as this section considers the use of soluble or non-soluble supports, rather than the reaction conditions which are useful for preparation of the library of PBM's associated with metal ions (see Jacobsen, page 39, lines 12-36).

In Example 1 of Jacobsen (pages 40-41 and Figure 2A), no detailed explanation of the reaction conditions for formation of the PBM library is provided; Jacobsen only cites to an endnote which explains that "[e]xperimental procedures for the synthesis of the library and its components are provided as supporting information." No such supporting information appears in the specification. However, Francis et al., "Combinatorial Approach to the Discovery of Novel Coordination Complexes," J. Am. Chem. Soc. 118:8983-8984, S2-9 (1996) ("Francis") (attached hereto as Exhibit 1), the underlying work for Jacobsen, is instructive as to the conditions employed therein. Specifically, at page S4 of Francis, the solid phase library synthesis is disclosed. In each step, non-aqueous and non-equilibrating conditions were employed, including dichloromethane, diisopropylethylamine (DIPEA) and dimethylformamide (DMF), or DIPEA and N-methylpyrrolidone (NMP) for the various peptide coupling reactions; dimethylaminopyridine for acid chloride monomer coupling reactions; DIPEA and NMP for isocyanate coupling reactions; and DIPEA and dichloroethane for most other monomer coupling reactions. None of these reactions involved an aqueous solution and none were equilibrating.

In Example 2 of Jacobsen (page 42 and Figures 4A-G), reactions conditions for PBM formation are, again, not specified. Francis offers no explanation here. However, as dipeptides are being formed, one of ordinary skill can only speculate that the above-noted

peptide coupling schemes in Francis were likely employed. When PBM's were exposed to metal ions, the reaction was performed in dichloromethane (Jacobsen, Figure 4B).

Examples 3-5 and 7-8 provide no further evidence contradicting the use of non-aqueous and non-equilibrating conditions as in Examples 1-2.

In Example 6 of Jacobsen (page 43 and Figures 7A-E), reactions conditions for carbamate formation (DIPEA and NMP), amide formation (DIPEA and DMF), acid and sulfonyl chloride end-capping (DIPEA and DCE), carboxylic acid end-capping (DIPEA and DMF), and isocyanate (DIPEA and NMP) are disclosed. In each of these non-equilibrating reactions, non-aqueous conditions were employed.

Thus, Jacobsen fails to teach or suggest the formation of a combinatorial library as presently claimed, "which exists at equilibrium in an aqueous solution or suspension including one or more metal atoms or metal ions and a group of three or more non-biopolymer ligands each of which comprises (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a biological receptor". More specifically, Jacobsen fails to teach or suggest a combinatorial library whose members are "formed of a metal atom or metal ion and at least two non-biopolymer ligands, wherein each of the at least two non-biopolymer ligands is reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond."

Because Jacobsen fails to teach or suggest each and every limitation of the presently claimed invention, Jacobsen fails to anticipate, nor would Jacobsen have rendered obvious, the presently claimed invention.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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APPENDIX
Version Showing Changes to the Amended Claims

1. (Twice Amended) A combinatorial library which exists at equilibrium in an aqueous solution or suspension including one or more metal atoms or metal ions and a group of three or more non-biopolymer ligands each of which comprises (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a biological receptor, the combinatorial library comprising:

a plurality of at least six different complexes in the aqueous solution or suspension, each of the plurality of at least six different complexes being formed of a metal atom or metal ion and at least two ~~of the~~ non-biopolymer ligands ~~each comprising (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a target molecule~~, wherein each of the at least two non-biopolymer ligands is reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond and wherein each different complex in said library has different ligands bonded to the metal atom or metal ion.